History of GIST

- Historically GIST have been misdiagnosed as leimyomas or leimyosarcomas based on morphology.
- Immunohistochemistry in the 1980's demonstrated that some of these tumors lacked features of smooth muscle differentiation, some had markers of neuronal differentiation and some had neither of the above markers.
- Mazur and Clark coined the term "gastrointestinal stromal tumors" to collectively refer a group of mesenchymal tumors of neurogenic or myogenic differentiation.
- The discovery of KIT led to the realization of GIST as a distinct entity from other non-epithelial GI tumors

Mazur MT, and Clark HB. Am J Surg Path 1983; 7: 507-19
Joensuu H, et al. Lancet Oncol 2002 ; 3 : 655-64

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Gastric stromal tumors

Reappraisal of histogenesis

ABSTRACT Twenty-eight gastric wall tumors classified by light microscopy as leiomyomas or leiomyosarcomas were reevaluated for histogenesis. Each case was analyzed for the presence of S-100 protein, a marker for cells derived from neuroectoderm, by the immunoperoxidase technique. Eight tumors contained cells with positive immunostaining for S-100 protein. Usually this staining was focal, but in one case staining was diffuse. In three additional cases the immunostaining outlined a nerve within the tumor. In contrast, two esophageal and 10 uterine leiomyomas, as well as normal gastric smooth muscle, gave negative reactions for S-100 protein. Twelve cases had tissue processed for electron microscopy. Only two of the tumors, one leiomyoma and one leiomyosarcoma, contained cytoplasmic myofilaments with densities expected in cells derived from smooth muscle; neither of these tumors stained for S-100 protein. In one case, the tumor with diffuse staining for S-100 protein, the cells resembled Schwann cells ultrastructurally. The remaining nine cases had neither smooth muscle nor Schwann cell features. They did contain interposed cell processes, primitive junctions, and large cytoplasmic vacuoles. The results of this study indicate that many gastric wall tumors are not derived from smooth muscle. The presence of S-100 protein suggests a nerve sheath origin in some cases. While the ultrastructure of many gastric tumors does not resemble nerve sheath cells in most peripheral nerves, the myenteric nervous system is a possible source for perineurial or mesenchymal nerve sheath cells with distinctive fine structure. Further study is needed to refine our knowledge of the histogenesis of gastric stromal tumors.

Am J Surg Pathol 7: 507–519, 1983.

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INTRODUCTION

The stromal tumors of the gastric wall generally are thought to originate from smooth muscle since they often have a prominent spindle-cell component and they involve the gastric musculature. Despite these reasonable assumptions, these neoplasms show light- and electron-microscopic features that are not commonly seen in leiomyomas and leiomyosarcomas arising in other sites. Specifically, by light microscopy gastric mesenchymal tumors often have epithelioid patterns, vacuolated cytoplasm, and nuclear palisading.[1–3,10,30,35]

Electron microscopy has shown that the component cells of gastric stromal tumors have cell processes and usually lack the typical microfilaments with densities, a hallmark of benign and malignant smooth muscle at other sites.[10,18,19,25,29,38–40] Because of these morphologic differences, some authors have suggested that gastric stromal tumors may originate from other mesenchymal cells,[3] although in the absence of additional knowledge of the exact type of progenitor cell, terminology applicable to smooth muscle has been retained.

The question of histogenesis has clinical relevance. Although it is generally possible to separate these tumors into benign and malignant categories,[2,28,30] investigators have found that these tumors tend to have less predictable biologic behavior, based on mitotic activity, than uterine smooth muscle tumors.[1,3,28] This clinical circumstance further suggests that these gastric tumors represent a unique and distinctive group of neoplasms that can be separated from leiomyomas and leiomyosarcomas.

Mazur and Clark. Am J Surg Pathol. 1983 Sep;7(6):507-19

KIT Receptor Tyrosine Kinase

- In 1986 a new acute transforming feline retrovirus, the Hardy-Zuckerman 4 feline sarcoma virus (HZ4-FeSV) was isolated from a feline fibrosarcoma.
- The viral genome of HZ4-FeSV contained a new oncogene that was designated v-kit. C-kit is the cellular homologue of the oncogene v-kit
- C-kit encodes a transmembrane tyrosine kinase receptor called KIT.

Nature 1988 Sep 1;335(6185):88-9

KIT Receptor Tyrosine Kinase

- Kit is a 145-KD glycoprotein which can be detected by immuno-histochemical staining for CD117
  - CD117 is an epitope on the extra-cellular domain of the Kit receptor
  - >95% of GIST are CD117 positive
- Steel factor (SLF), also known as stem-cell factor, is the ligand for Kit
  - Binding of SLF to Kit results in receptor homo-dimerization, activation of KIT tyrosine kinase activity, and resultant phosphorylation of a variety of substrates that serve as effectors of intracellular signal transduction.
  - GIST have characteristic gain of function mutations which result in ligand-independent activation of signal transduction

Hirota S, et al. Science 1998; 279:577-80; Kindblom LG, et al. Am J Pathol 1998; 152:1259-69.
Rubin BP, et al. Cancer Res 2001; 61: 8118-21; de Silva MVC, et al. Pathol Oncol Res 2003; 9: 13-19.

cules, CA). After 24 hours, selection was initiated by addition of G418 (400 μg/ml) to the cell culture medium. A stable clone 9 cell line overexpressing GFP-Dyn2 was achieved within a month.

12. Clone 9 cells were maintained at 37°C in Ham's F-12K medium supplemented with 10% fetal bovine serum. Cells were grown on cover glasses for 1 to 3 days before microscopy.
13. For immunolocalization, cells were fixed in aldehyde and then labeled as described (*9*) and mounted in ProLong antifade reagent (Molecular Probes, Eugene, OR). Alternatively, live cells were viewed directly. Either an epifluorescence microscope (Axiovert 35, Carl Zeiss) equipped with a 100-W mercury arc (attenuated up to 90%) and a cooled charged coupled device (CCD) camera (SenSys, Photometrics, Tucson, AR) or a confocal laser scanning microscope (LSM-410, Carl Zeiss) was used for fluorescence microscopy.
14. The location of each peptide used as antigen within the dynamin molecule is shown in Fig. 3B. The Pan-dynamin MC63 antibody has been shown to specifically recognize a 100-kD dynamin band in rat liver fractions by immunoblotting and immunoprecipitation (*9*). The Pan-dynamin MC60 and Dyn2-specific antibodies also have been characterized (*27*). The antibodies added to cell-free assays were affinity purified and concentrated (~3 mg/ml); then they were tested by immunoblot analysis to confirm retention of activity (*9*). Antiserum against clathrin was produced from the hybridoma X22 (ATCC). The antibodies against the cytoplasmic and luminal domains of the pIgA-R have been described (*19*). The rabbit polyclonal antibody to TGN38 was to a peptide representing the COOH-terminal cytoplasmic portion of the protein.
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16. S. M. Jones, K. E. Howell, J. R. Henley, H. Cao, M. A. McNiven, data not shown.
17. R. S. Taylor, S. M. Jones, R. H. Dahl, M. H. Nordeen, K. E. Howell, *Mol. Biol. Cell* **8**, 1911 (1997).
18. For the membrane binding assay, stacked Golgi fractions (SGF1) were isolated from rat liver (*17*). SGF1 (100 μg) plus cytosol (200 μg) were incubated in 25 mM Hepes (pH 6.7), 25 mM KCl, 1.5 mM magnesium acetate in a final volume of 1.0 ml at 37°C for 15 min. For assay mixtures that contained ATP, 1.0 mM ATP and an ATP regenerating system (8.0 mM creatine phosphate, 0.043 mg of creatine phosphokinase per milliliter) were added to the reaction mixture. For other assays GTP-γ-S was added to a final concentration of 10.0 μM. After incubation, the reaction mixture was loaded onto a 0.5 M sucrose cushion and centrifuged in a TLS55 rotor at 55,000 rpm for 1 hour. Membrane pellets were resolved by SDS-PAGE, transferred to nitrocellulose filters, immunoblotted with antibodies against dynamin (MC63), which were detected with ^{125}I-labeled protein A (NEN, Boston, MA), and exposed to film for autoradiography. Immunoblots were quantitated with a PhosphorImager (Molecular Dynamics, Sunnyvale, CA).
19. J. Salamero, E. S. Sztul, K. E. Howell, *Proc. Natl. Acad. Sci. U.S.A.* **87**, 7717 (1990).
20. The cell-free assay of budding from immobilized stacked Golgi fractions was carried out as described (*24*). Each assay mixture contained a 2.5-mg magnetic core and shell beads with ~50 μg of the stacked Golgi fraction immobilized. The immobilized fraction has been characterized (*24*). For the budding reaction, the immobilized fraction was incubated in 2.5 ml containing cytosol at 0.70 mg/ml, 25 mM Hepes (pH 6.7), 25 mM KCl, 1.5 mM magnesium acetate, 1.0 mM ATP, an ATP regenerating system (8.0 mM creatine phosphate, 0.043 mg of creatine phosphokinase per milliliter), and 5 mg of bovine serum albumin (BSA) per milliliter (final concentrations). For cell-free assays in which antibodies were tested, increasing concentrations of antibody were incubated with the cytosol for 30 min on ice before addition to the cell-free assay. After 10 min at 37°C the Golgi fraction remaining on the beads was retrieved, and the budded vesicles remained in the supernatant. The budded fraction was pelleted through a 0.25 M sucrose cushion (100,000*g* for 1 hour) to deplete the BSA (5 mg/ml) and large amounts of cytosolic proteins. The pellet was resuspended in gel sample buffer and resolved by SDS-PAGE. Budding efficiency was reported as the percentage of the total mature sialylated pIgA-R (116 kD) present in the budded fraction (100% represents the amount present in the immobilized SGF before budding). The pIgA-R distribution was determined by quantitative immunoblotting of the fractions from the cell-free assay. Because the pIgA-R is a plasma membrane receptor synthesized in relatively high amounts in rat liver (*28*), it defines a specific population of constitutive exocytic vesicles (*24*). The amount of clathrin-coated vesicle formation was assessed by determining the amount of clathrin heavy chain in the total budded vesicle fraction by quantitative immunoblotting with monoclonal antibody TD.1 (ATCC). Percentage budding was calculated as the amount of clathrin heavy chain in the pelleted total budded fraction compared with that found in control budding reactions (100%). The amount of clathrin-coated vesicle budding in the absence of ATP and cytosol was 3%.
21. S. M. Jones, K. E. Howell, J. R. Henley, H. Cao, M. A. McNiven, data not shown.
22. For depletion of dynamin proteins from rat liver cytosol, 2 ml of rat liver cytosol (16 mg/ml), prepared by the methods of Palade and coworkers (*28*), was passed repeatedly over an MC63 Pan-dynamin antibody column at 4°C. The cytosolic void volume next was passed repeatedly over a Dyn2-specific antibody column at 4°C. The void volume was concentrated, separated by SDS-PAGE, and immunoblotted with dynamin antibodies to confirm a complete depletion of dynamin proteins from the cytosol. The dynamin antibody columns were prepared by immobilizing 9.3 mg and 4.9 mg of affinity-purified MC63 or Dyn2-specific antibodies, respectively, per 1.5-ml column matrix. All antibodies were immobilized by using an Immunopure protein A IgG orientation kit (Pierce Chemical, Rockford, IL) according to the manufacturer's instructions.
23. A dynamin-enriched fraction was isolated from freshly obtained rat brains according to established methods (*9*, *29*). Briefly, a rat brain homogenate was passed through a 10-ml DEAE anion-exchange column and then added to a 5-ml phosphocellulose column. After substantial rinsing in 100 mM NaCl buffer, dynamin proteins were eluted from the column with 250 mM NaCl, and then the fractions were pooled, concentrated, dialyzed, and frozen in liquid nitrogen.
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30. At UCHSC the use of the Hepatobiliary Center, Cell Biology Core (NIH, P30 DK-34914), and the Cancer Center Monoclonal Antibody Facility (P30 CA-46934) is acknowledged. We especially thank J. Ugelstad and R. Schmid, SINTEF, University of Trondheim, Norway, for the shell and core magnetic beads used in the cell-free assay. Thanks also goes to F. Garcia for her help with the GFP expression studies, to E. Krueger for his work on the GFP imaging, and to B. Oswald for help with preparation of antibodies and depleted cytosol.

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Gain-of-Function Mutations of c-*kit* in Human Gastrointestinal Stromal Tumors

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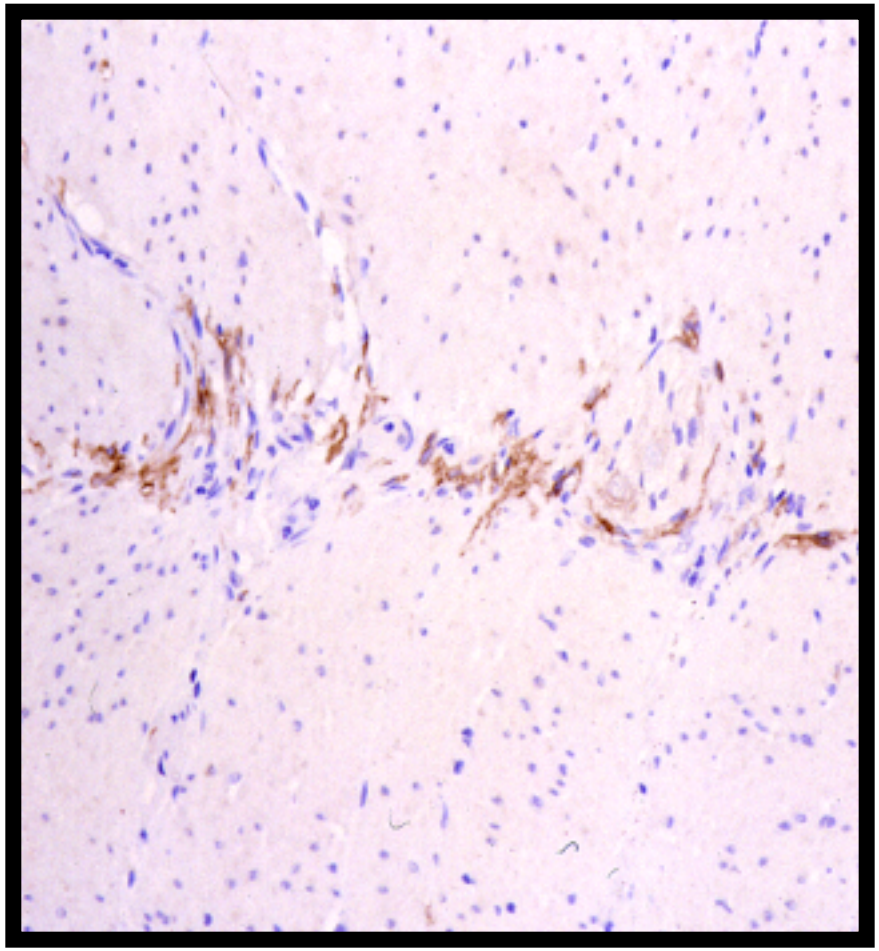
Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors in the human digestive tract, but their molecular etiology and cellular origin are unknown. Sequencing of c-*kit* complementary DNA, which encodes a proto-oncogenic receptor tyrosine kinase (KIT), from five GISTs revealed mutations in the region between the transmembrane and tyrosine kinase domains. All of the corresponding mutant KIT proteins were constitutively activated without the KIT ligand, stem cell factor (SCF). Stable transfection of the mutant c-*kit* complementary DNAs induced malignant transformation of Ba/F3 murine lymphoid cells, suggesting that the mutations contribute to tumor development. GISTs may originate from the interstitial cells of Cajal (ICCs) because the development of ICCs is dependent on the SCF-KIT interaction and because, like GISTs, these cells express both KIT and CD34.

The c-*kit* proto-oncogene encodes a type III receptor tyrosine kinase (KIT) (*1*), the ligand of which is SCF (*2*). SCF-KIT interaction is essential for development of melanocytes, erythrocytes, germ cells, mast cells and ICCs (*3*, *4*). Gain-of-function mutations of the c-*kit* gene have been found in several tumor mast cell lines of rodents and humans (*5*, *6*) and in mast cell tumors of humans (*7*). Here we investigate the mutational status of c-*kit* in mesenchymal tumors of the human gastrointestinal (GI) tract.

Hirota et al. Science. 1998 Jan 23;279(5350):577-80.

Interstitial Cells of Cajal as a Precursor to GIST



- Innervated network of KIT+ cells, amidst GI smooth muscle
- Pacemaker function coordinates peristalsis
- Absence of KIT function results in aperistalsis

Kindblom LG, et al. Am J Pathol 1998; 152:1259-69.
Hirota S, et al. Science 1998; 279:577-80

American Journal of Pathology, Vol. 152, No. 5, May 1998

Gastrointestinal Pacemaker Cell Tumor (GIPACT)

Gastrointestinal Stromal Tumors Show Phenotypic Characteristics of the Interstitial Cells of Cajal

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The interstitial cells of Cajal (ICC) form a complex cell network within the gastrointestinal tract wall where they function as a pacemaker system. Expression of the kit proto-oncogene is essential for the development of this system. The aim of our study was to examine the hypothesis that gastrointestinal stromal tumors differentiate toward cells with an ICC phenotype. Ultrastructurally, 58 stromal tumors were characterized and found to share many features with ICC. Seventy-eight stromal tumors were immunophenotyped, particularly with regard to the kit receptor. All 78 tumors revealed strong, homogeneous immunoreactivity for the kit receptor as did ICC of adjacent and control gastrointestinal walls. Focal hyperplasia and hypertrophy of kit receptor positive cells were also observed in the gastrointestinal wall adjacent to the tumors. CD34 immunoreactivity observed in interstitial cells surrounding Auerbach's ganglia suggests that a subpopulation of ICC is CD34 positive and may explain why 56 of 78 stromal tumors were CD34 positive. Thirty control tumors, including gastrointestinal leiomyomas and leiomyosarcomas, were all negative for the kit receptor. We conclude that gastrointestinal stromal tumors show striking morphological and immunophenotypic similarities with ICC and that they may originate from stem cells that differentiate toward a pacemaker cell phenotype. We propose that the noncommittal name "gastrointestinal stromal tumor" be replaced by gastrointestinal pacemaker cell tumor. *(Am J Pathol 1998, 152:1259–1269)*

Despite numerous studies, gastrointestinal stromal tumors remain problematic with regard to origin, differentiation, nomenclature, and prediction of prognosis. Their morphological spectrum is wide, ranging from bland to frankly malignant tumors with spindled and/or epithelioid appearances.[1–3] Hence, a variety of names such as epithelioid or bizarre leiomyomas, epithelioid leiomyosarcomas or leiomyoblastomas, and gastrointestinal autonomic nerve tumors (GANT) have been used for these tumors reflecting the various views regarding their differentiation, classification, and prognosis.[1–8] The noncommittal term gastrointestinal stromal tumor has recently gained wide acceptance, emphasizing their enigmatic origin and the fact that most of these lesions do not display convincing smooth muscle or neuronal differentiation.[2,9,10]

The existence of a complex system of interstitial cells of Cajal (ICC), which are intercalated between the autonomic nerves and the muscle walls of the gastrointestinal tract, has been known for over 100 years.[11] Detailed morphological and electrophysiological studies in many species, including humans, have indicated that ICC have a pacemaker function.[11–18] Recently, ICC were found to express the kit proto-oncogene, which encodes for a transmembrane tyrosine-kinase receptor (CD117) and has the stem cell factor as its ligand. Expression of the kit gene is essential for the development of normal hematopoiesis, proliferation, and migration of primordial germ cells and melanoblasts during embryogenesis as well as for the development of the ICC and gastrointestinal pacemaker activity.[19–28] A cluster of human type III receptor protein tyrosine kinase genes, including the kit gene, has been mapped to chromosome 4q11-q12.[29]

The present study was designed to test the hypothesis that gastrointestinal stromal tumors differentiate toward an ICC phenotype. Ultrastructural examination and immunohistochemical analysis for the kit tyrosine-kinase receptor (CD117) was performed in a large series of well-characterized stromal tumors along with appropriate normal tissues and tumor controls. The results of this study support our hypothesis that gastrointestinal stromal tumors originate from a stem cell that differentiates toward an ICC phenotype.

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Kindblom et al. Am J Pathol. 1998 May;152(5):1259-69.

Gastrointestinal Stromal Tumors

- Around 5,000 to 6,000 new cases each year
- Tends to occur in middle aged persons with a slight male predilection
- Occur throughout the GI tract
  - Stomach 50-60%
  - Small bowel 20-30%
  - Large bowel 10%
  - Esophagus 5%
  - Elsewhere in abdomen 5%

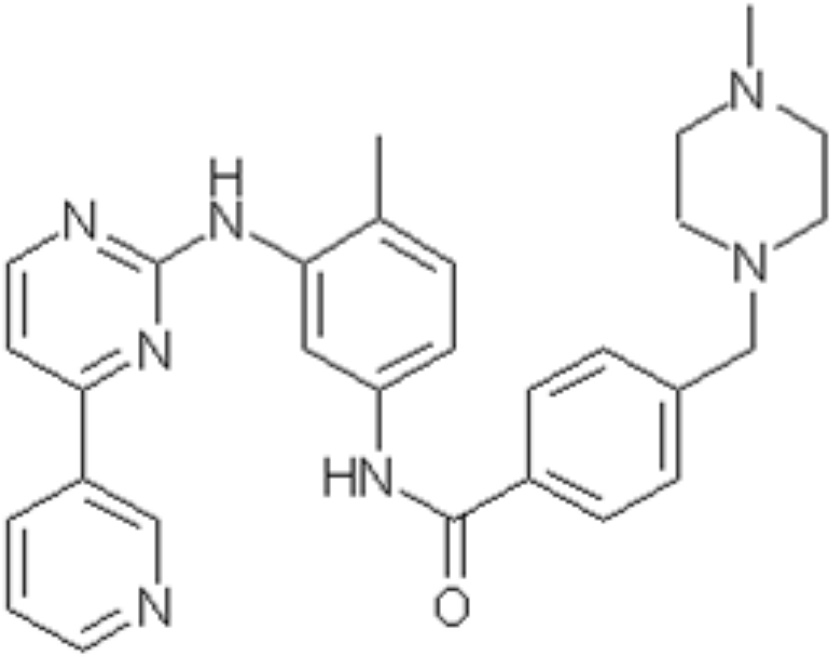
DeMatteo RP, et al. Ann Surg 2000; 231:51-8

Prognosis of GIST

- The 5-year survival for malignant GIST varies widely and has been reported to be from 28 to 60%.
- Median survival times
  - Unresectable disease: 10–23 months.
  - Metastatic or recurrent disease: 12 -19 months.

Joensuu H, et al. Lancet Oncol 2002 ; 3 : 655-64

Imatinib Mesylate



- Inhibits intracellular kinase domains of ABL, KIT, and PDGFR
- Abrogates kinase signaling by inhibition of ATP binding and substrate docking

Fletcher L. Nat. Biotechnol. 2001; 19:599-600

„patient zero“

The New England Journal of Medicine

Brief Report

Effect of the Tyrosine Kinase Inhibitor STI571 in a Patient with a Metastatic Gastrointestinal Stromal Tumor

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GASTROINTESTINAL stromal tumors are a group of mesenchymal neoplasms that arise from precursors of the connective-tissue cells of the gastrointestinal tract.[1] They occur predominantly in middle-aged and older persons, and approximately 70 percent of the tumors are found in the stomach, 20 to 30 percent are found in the small intestine, and less than 10 percent are found elsewhere in the gastrointestinal tract.[1] Recent studies have shown that cells in gastrointestinal stromal tumors express a growth factor receptor with tyrosine kinase activity termed c-kit. This receptor, the product of the proto-oncogene c-*kit*, can be detected by immunohistochemical staining for CD117, which appears to be the most specific diagnostic criterion for the diagnosis of gastrointestinal stromal tumors.[2] The ligand for the c-kit receptor is stem-cell factor, also known as steel factor or c-kit ligand.[3] Mutations of c-*kit* that cause constitutive activation of the tyrosine kinase function of c-kit are detectable in most gastrointestinal stromal tumors and appear to play a central part in the pathogenesis of these tumors.[4,5] These mutations result in ligand-independent tyrosine kinase activity, autophosphorylation of c-kit, uncontrolled cell proliferation, and stimulation of downstream signaling pathways, including those involving phosphatidylinositol 3-kinase and mitogen-activated protein kinases. Gastrointestinal stromal tumors are notoriously unresponsive to cancer chemotherapy, and there is no effective therapy for advanced, metastatic disease.[6]

We used STI571 (Glivec, Novartis, Basel, Switzerland),[7] an inhibitor of the tyrosine kinase activity of c-kit, in a patient with a gastrointestinal stromal tumor.

CASE REPORT

In October 1996, a 50-year-old, previously healthy woman presented with mild abdominal discomfort and a large mass in the upper abdomen. Two tumors, 6.5 and 10 cm in diameter, were removed from the stomach by proximal gastric resection, and the greater omentum and mesocolic peritoneum were removed because of the presence of multiple metastatic nodules 1 to 2 mm in diameter. Histologic examination of the specimens revealed more than 20 cells undergoing mitosis per 10 high-power fields and identified the masses as a gastrointestinal stromal tumor. The diagnosis was confirmed by immunostaining for CD117, and a c-*kit* mutation consisting of a deletion of 15 bp from exon 11 was detected in tumor DNA amplified by the polymerase chain reaction.[8]

Recurrent tumors in the left upper abdomen, two liver metastases, and multiple small intra-abdominal metastases were excised in February 1998, and in September 1998 six more liver metastases and an ovarian metastasis were removed. Seven cycles of chemotherapy with mesna, doxorubicin, ifosfamide, and dacarbazine were given from November 1998 to March 1999 for additional liver metastases, but there was no clinical response. In March 1999, progression of the disease prompted removal of a metastasis that was obstructing the large bowel and 45 smaller metastases by laparotomy. The patient was treated between April 1999 and February 2000 with 400 mg of thalidomide once daily and 900,000 U of subcutaneous interferon alfa three times a day, but by Febru[illegible] 2000 the liver metastases were progressing in size and [illegible] and several new intra-abdominal and mesenteri[illegible] documented by magnetic resonance im[illegible]

The patient then agreed to participate in this study of STI571. The institutional review board of the Helsinki University Central Hospital approved the study, and the patient gave written informed consent. Treatment with four 100-mg capsules of STI571 once daily was started in March 2000. This dose was based on evaluations of the safety and tolerability of STI571 in patients with chronic myeloid leukemia.[9] Toxicity was assessed at follow-up visits every two to four weeks, and blood-cell counts and blood chemical values were analyzed every one to two weeks. The response to treatment was assessed with dynamic MRI, positron-emission tomography (PET) with [^{18}F]fluorodeoxyglucose as a tracer, and serial needle biopsies of a liver metastasis.

METHODS

Immunostaining for CD117 was performed with a polyclonal rabbit antibody (sc-168, Santa Cruz Biotechnology, Santa Cruz, Calif.) diluted 1:200 and for Ki-67 antigen, a marker of cell proliferation, with another polyclonal rabbit antibody (A0047, Dako, Glostrup, Denmark) diluted 1:150. Staining was analyzed with a detection kit (ChemMate Peroxidase/DAB, Dako) designed to be used with an automated immunostaining system (TechMate 500 Medical Systems, Ventana, Tucson, Ariz.).

RESULTS

Evaluation of the Response by MRI

When measured as the sum of the products of two perpendicular axes of each of eight large liver metastases, the size of the tumor one day before the start of treatment with STI571 was 112.5 cm^2. On subsequent MRI scans, the size of the tumor was as fol-

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Drs. Joensuu and Roberts contributed equally to the article.

Treatment with four 100 mg capsules of STI571 once daily was started in March 2000.

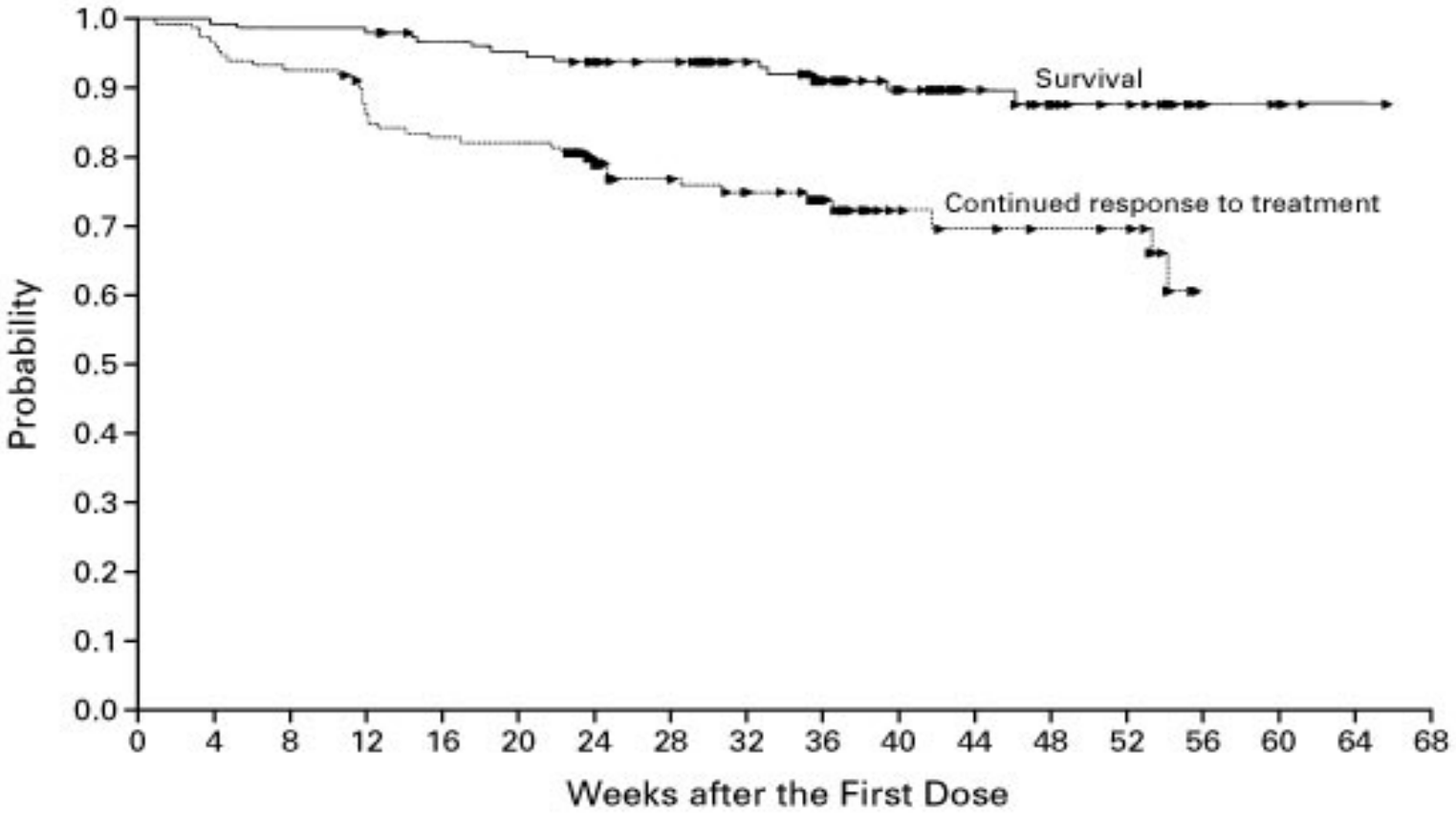
Imatinib Mesylate in Advanced/Unresectable GIST

	400 Mg N = 73	600 Mg N = 74	Either Dose N = 147
Response Rate	49%	58%	54%
Stable Disease	32%	24%	28%

- This trial led to the approval of imatinib mesylate for GIST in February, 2002

Demetri GD et al. N Engl J Med 2002; 347: 472-80

Time to Progression and Survival



Demetri GD et al. N Engl J Med 2002; 347: 472-80

Studies of Imatinib Therapy in GIST

Pilot	Phase 1	Phase 2	Phase 3
Pilot Study Exploratory Study (N = 1)[1]	**Dose-Finding Study (N = 40)[2]**	**B2222 Open-Label Study (N = 147)[3]**	**EORTC 62005 Randomized Study (N = 946)[5]**
• 1 patient • 400 mg/d	• Efficacy and safety • 400 vs 1000 mg/d • Metastatic GIST (EORTC)	• Efficacy and safety • 400 vs 600 mg/d • Metastatic or unresectable GIST	• Efficacy and safety • 400 vs 800 mg/d • Metastatic or unresectable KIT-positive GIST
		EORTC phase 2 study (N = 51)[4]	**US Intergroup S0033 Study (N = 746)[6]**
		• Efficacy and safety • Advanced or metastatic GIST and other soft-tissue sarcomas	• Efficacy and safety • 400 vs 800mg/d • Metastatic or unresectable KIT-positive GIST

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Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial

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Lancet 2004; 364: 1127–134
See Comment page 1101
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Summary

Background Imatinib is approved worldwide for use in gastrointestinal stromal tumours (GIST). We aimed to assess dose dependency of response and progression-free survival with imatinib for metastatic GIST.

Methods 946 patients were randomly allocated imatinib 400 mg either once or twice a day. Those assigned the once a day regimen who had progression were offered the option of crossover. The primary endpoint was progression-free survival. Analysis was by intention to treat.

Findings At median follow-up of 760 days (IQR 644–859), 263 (56%) of 473 patients allocated imatinib once a day had progressed compared with 235 (50%) of 473 who were assigned treatment twice a day (estimated hazard ratio 0·82 [95% CI 0·69–0·98]; p=0·026). Side-effects arose in 465/470 (99%) patients allocated the once daily regimen compared with 468/472 (99%) assigned treatment twice a day. By comparison with the group treated once a day, more dose reductions (77 [16%] vs 282 [60%]) and treatment interruptions (189 [40%] vs 302 [64%]) were recorded in patients allocated the twice daily regimen, but treatment in both arms was fairly well tolerated. 52 (5%) patients achieved a complete response, 442 (47%) a partial response, and 300 (32%) stable disease, with no difference between groups. Median time to best response was 107 days (IQR 58–172).

Interpretation If response induction is the only aim of treatment, a daily dose of 400 mg of imatinib is sufficient; however, a dose of 400 mg twice a day achieves significantly longer progression-free survival.

Introduction

Gastrointestinal stromal tumours (GIST) are a subgroup of soft-tissue sarcomas with an estimated prevalence of 15–20 per 1 000 000.[1,2] These tumours are thought to arise from Cajal cells in intestinal walls, which are important for intestinal motor function.[3,4] GIST were previously classified as leiomyoma, leioblastoma, or leiomyosarcoma. They are insensitive to conventional chemotherapy[5] and are generally characterised by a gain-of-function mutation of the KIT receptor[6] and, occasionally, of the platelet-derived growth factor receptor α.

The clinical activity of imatinib—a small-molecule tyrosine-kinase inhibitor active against BCR-ABL, KIT, and platelet-derived growth factor—has been confirmed in GIST, both in an EORTC (European Organisation for Research and Treatment of Cancer) phase I study,[7] in which the highest feasible dose of imatinib was identified as 400 mg twice a day, and in phase II studies with doses of 400–800 mg daily.[8,9] Imatinib is approved worldwide for use in GIST, with a usual recommended dose of 400 mg daily. However, we still do not know whether the highest feasible daily dose yields a higher initial response rate or a better progression-free survival than the recommended dose. For this reason, we did a randomised trial to compare imatinib 400 mg once a day with 400 mg twice daily.

Patients and methods

Patients

Between February, 2001, and February, 2002, we recruited patients from 56 hospitals in 13 countries from Europe, Australia, New Zealand, and Singapore into our study. Eligibility criteria included histologically proven advanced or metastatic GIST characterised by c-KIT expression (assessed by DAKO immunohistochemical assay). Patients were not required to have measurable disease, and we did not need histological re-confirmation of malignant disease. Previous chemotherapy was accepted but should have been discontinued for more than 4 weeks. Other eligibility criteria included: age 18 years or older; WHO performance status less than 4; absolute neutrophil count greater than $1·5\times10^9$/L; platelet count greater than 100×10^9/L; serum creatinine up to 1·5 times the upper limit of normal (average 180 μmol/L); and total bilirubin less than 1·5 times the upper limit of normal (average 30 μmol/L). The study protocol was approved by institutional review boards according to applicable laws in all participating countries. All patients gave written informed consent.

Procedures

Within 14 days before we started treatment, we did a physical examination and complete blood count, including differential, platelets, and serum chemistry (bilirubin, creatinine, aspartate transaminase, alanine

Verweij et al. Lancet. 2004 Sep 25-Oct 1;364(9440):1127-34

Progression-Free Survival according to muational status

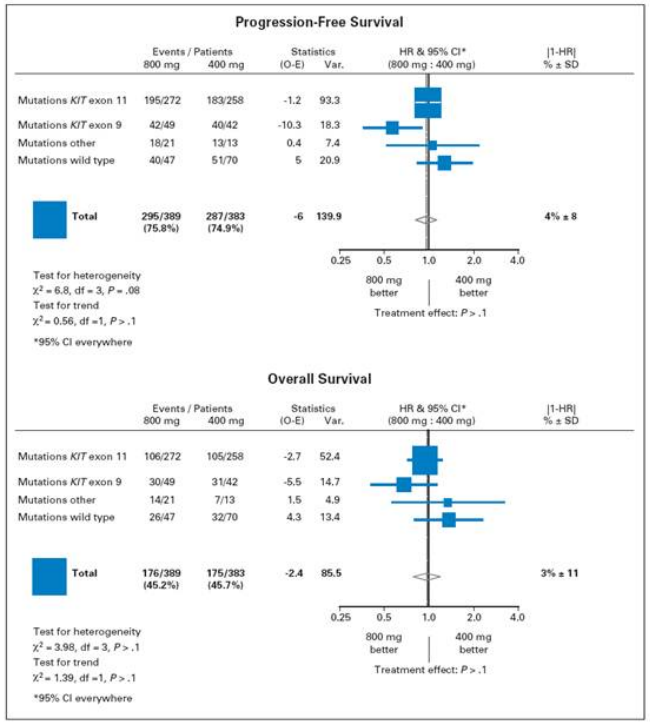
VOLUME 28 · NUMBER 7 · MARCH 1 2010

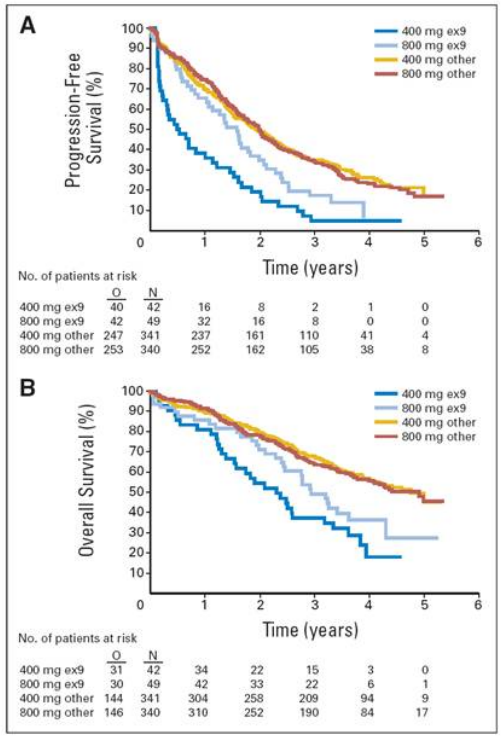
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Comparison of Two Doses of Imatinib for the Treatment of Unresectable or Metastatic Gastrointestinal Stromal Tumors: A Meta-Analysis of 1,640 Patients

Gastrointestinal Stromal Tumor Meta-Analysis Group (MetaGIST)





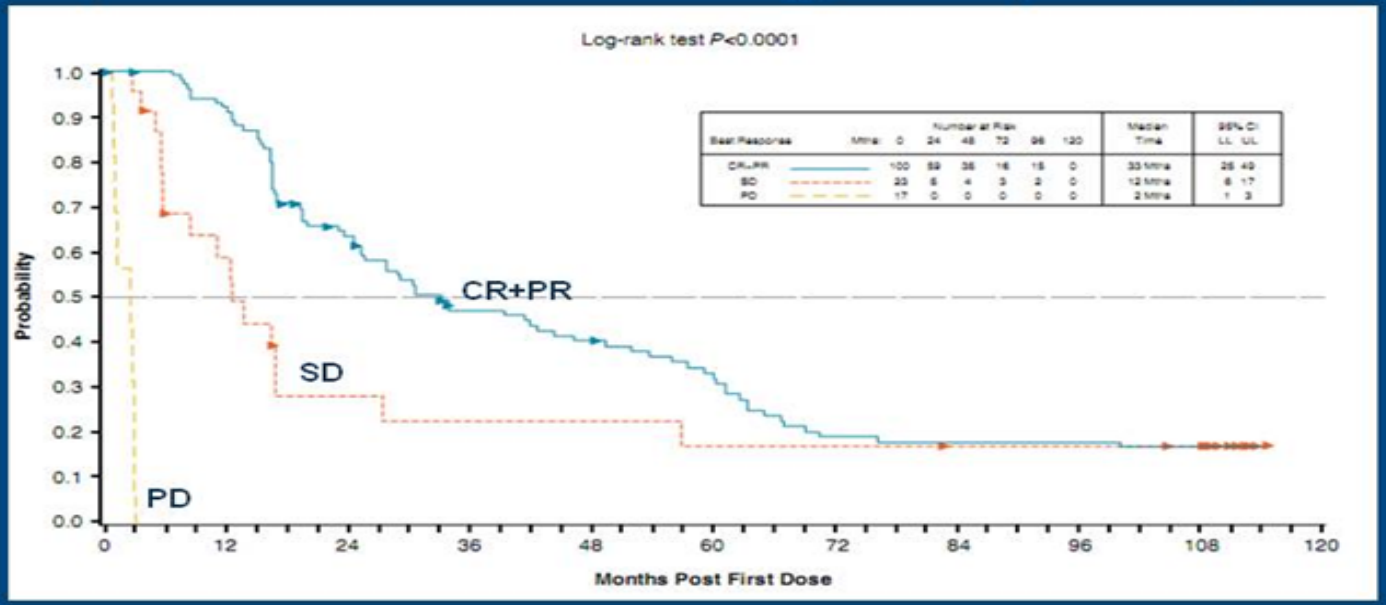
Follow-up results after 9 years of the ongoing, phase II B2222 trial of imatinib mesylate in patients with metastatic or unresectable KIT+ gastrointestinal stromal tumors (GIST)

M. von Mehren et al., J Clin Oncol 29: 2011 (suppl; abstr 10016)

Results

- PFS at 9 yrs was similar for patients with CR/PR (16%) or SD (17%) as best overall SWOG response

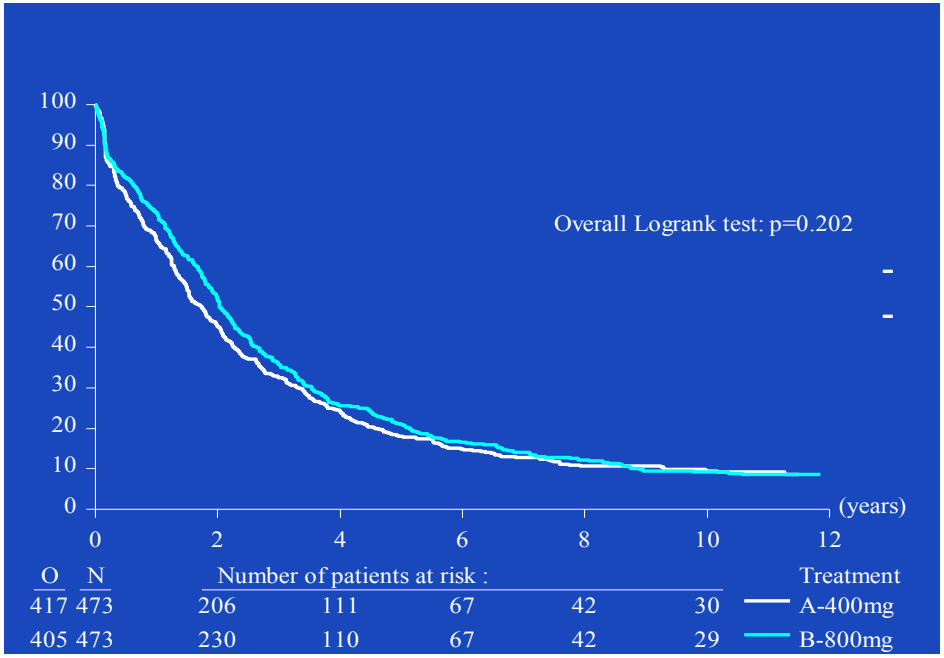
Kaplan-Meier Estimate of Time to Progression by Best Response

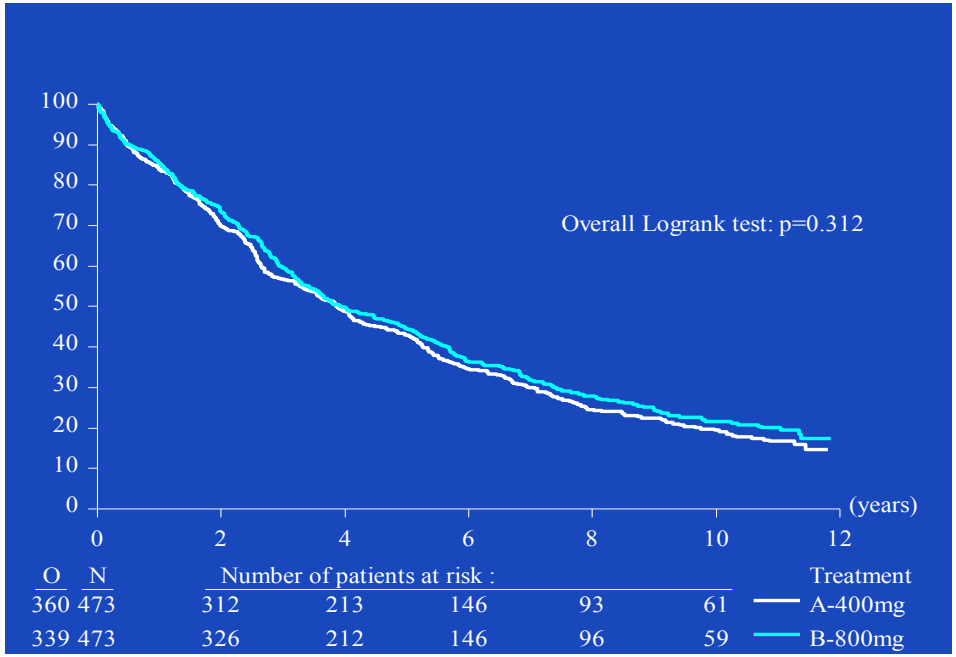


von Mehren *et al.* Abstract #10016.

PRESENTED AT: ASCO Annual '11 Meeting

EORTC 62005: PFS / OS





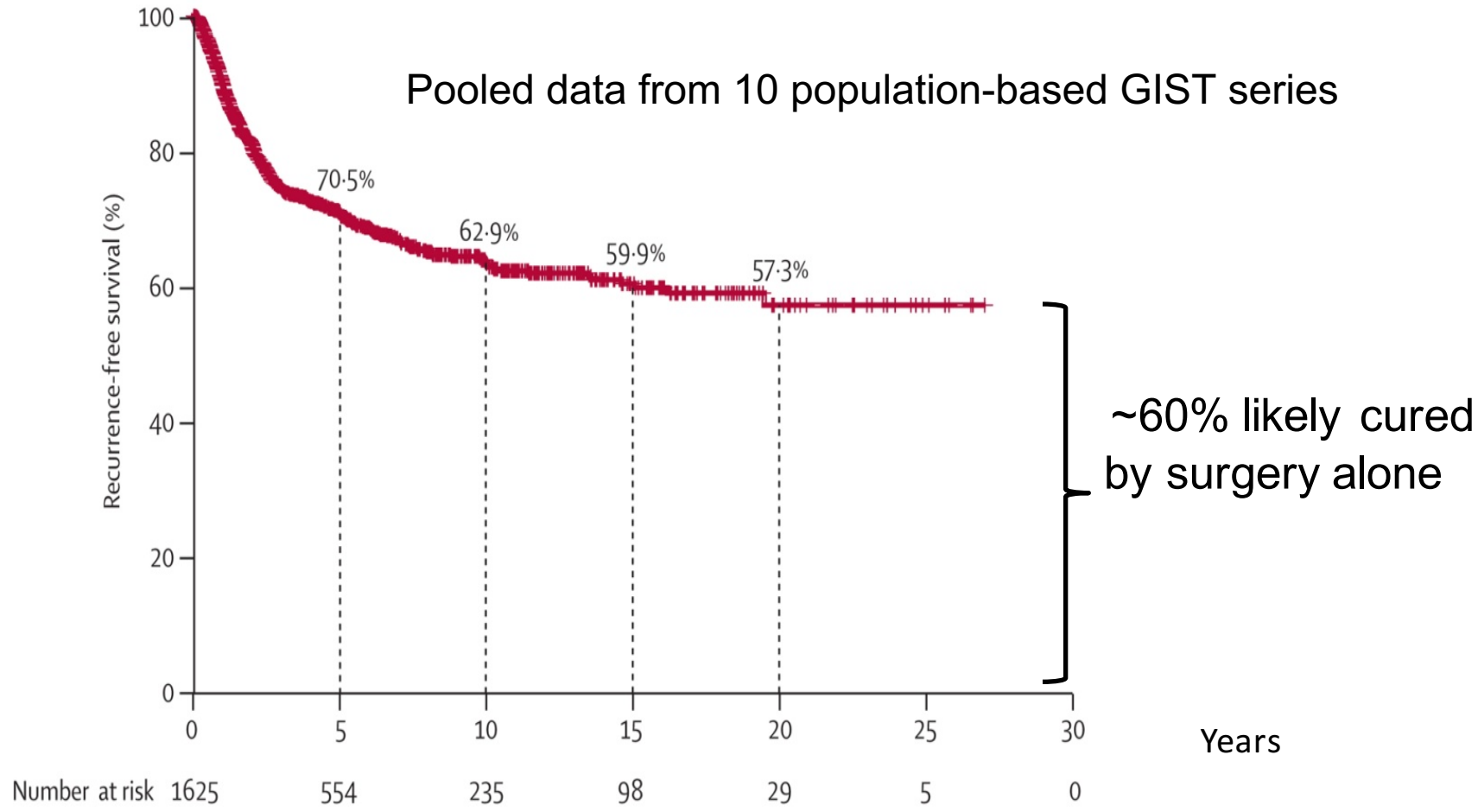
Casali PG et al., CTOS 2013

Overall Survival Estimates for Advanced GIST patients on S0033 treated with imatinib

Survival (years)	OS Estimate	95% CI
5	46%	43% - 50%
6	39%	36% - 43%
7	35%	31% - 38%
8	31%	28% - 35%
9	26%	23% - 30%
10	22%	19% - 26%

7

Risk of recurrence after surgey alone



Joensuu et al. Lancet Oncol 2012; 13:265-74

AFIP Risk Group Classification

Group	Group definition	Patients with progressive disease during long-term follow-up			
		Gastric %	Jejunal %	Duodenal %	Rectal %
1	≤2.0 cm, ≤5/50 HPF	0	0	0	0
2	2.1-5.0 cm, ≤5/50 HPF	1.9	4.3	8.3	8.5
3a	5.1-10.0 cm, ≤5/50 HPF	3.6	24		
3b	>10.0 cm, ≤5/50 HPF	12	52	34*	57*
4	≤2.0 cm, >5/50 HPF	0*	50*	-	54
5	2.1-5.0 cm, >5/50 HPF	16	73	50	52
6a	5.1-10.0 cm, >5/50 HPF	55	85		
6b	>10.0 cm >5/50 HPF	86	90	86*	71*

*very low numbers

Miettinen M, Lasota J., Sem Diagn Pathol 2006;23:70-83

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3b	>10.0 cm, ≤5/50 HPF	12	52	34*	57*
4	≤2.0 cm, >5/50 HPF	0*	50*	-	54
5	2.1-5.0 cm, >5/50 HPF	16	73	50	52
6a	5.1-10.0 cm, >5/50 HPF	55	85		
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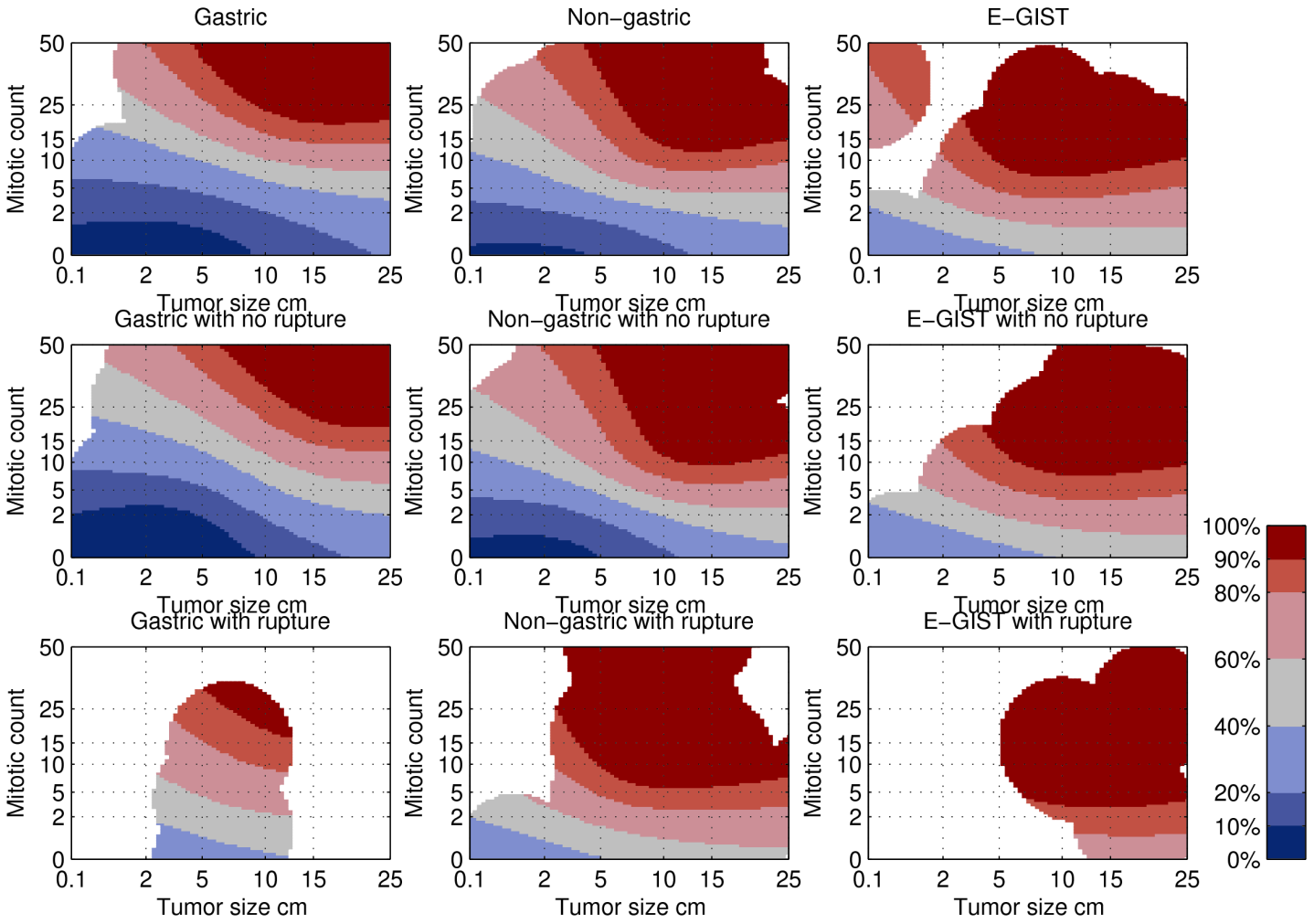
Miettinen M, Lasota J., Sem Diagn Pathol 2006;23:70-83

Prognostic contour maps, 10-year RFS

Rupture ?

No rupture

Rupture present

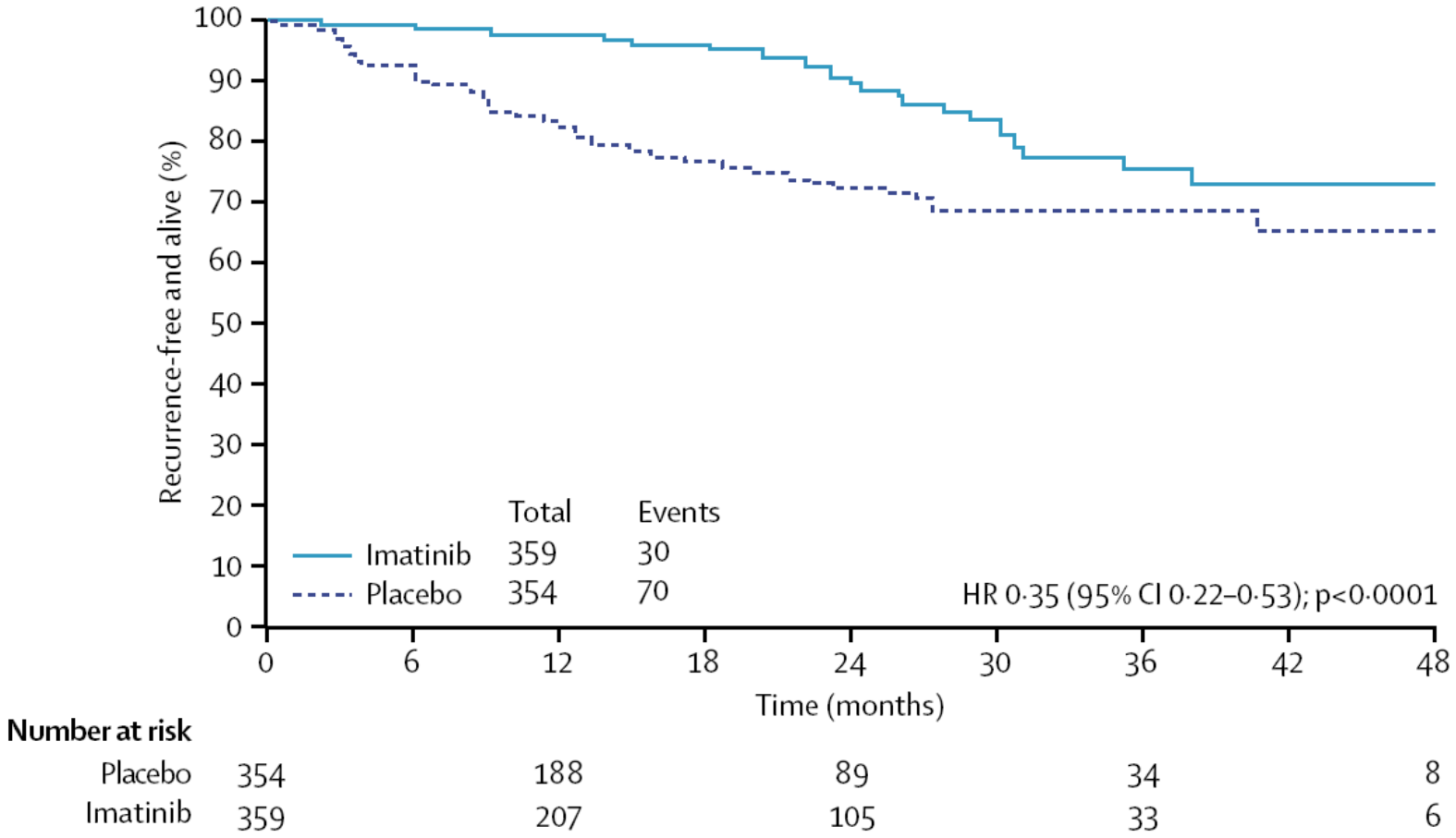


Joensuu et al. Lancet Oncol 2012; 13:265-74

Adjuvant Imatinib Therapy for GIST: Rationale

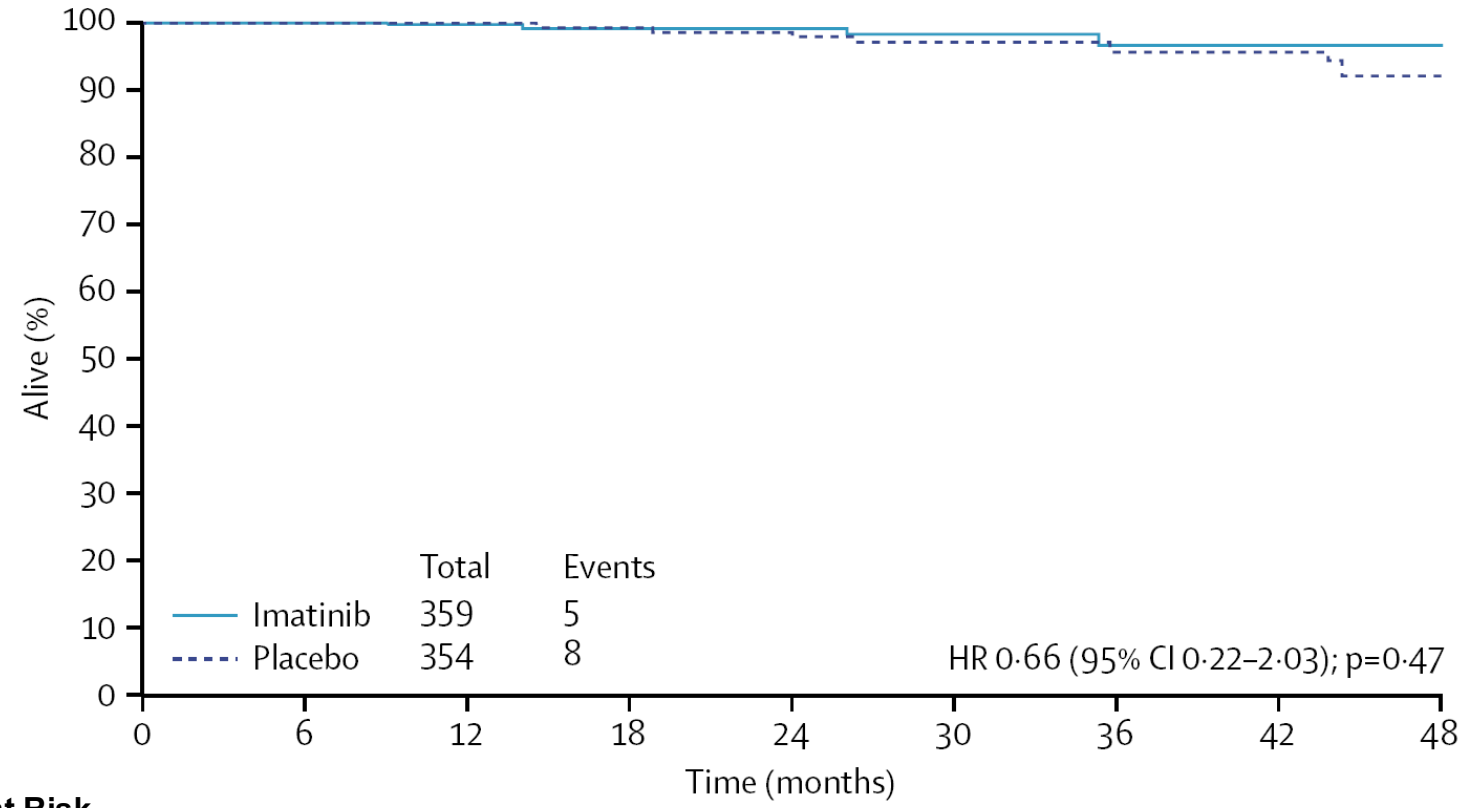
- High rates of recurrence after resection, especially in patients with high-risk GIST
- Imatinib represents effective oral therapy with a low toxicity profile and may be effective as an adjuvant to surgery in
  - Treatment of low-volume microscopic disease
- Randomised trials investigating use of imatinib in an adjuvant setting
  - ACOSOG Z9001 *(ASCO 2007, Lancet 2009)*
  - SSGXVIII *(ASCO 2011, JAMA 2012)*
  - EORTC 62024

Z9001: Recurrence-Free Survival



DeMatteo et al. Lancet. 2009;373:1097-1104.

Z9001: Overall Survival



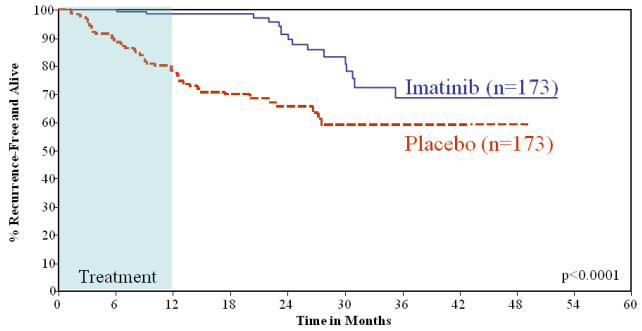
Number at Risk

Placebo	354	241	151	58	15
Imatinib	359	226	137	51	15

DeMatteo et al. Lancet. 2009;373:1097-1104.

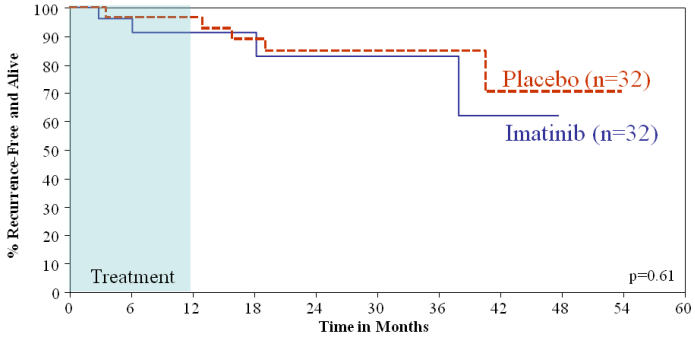
Influence of mutational status on outcome of adjuvant imatinib

RFS for Exon 11

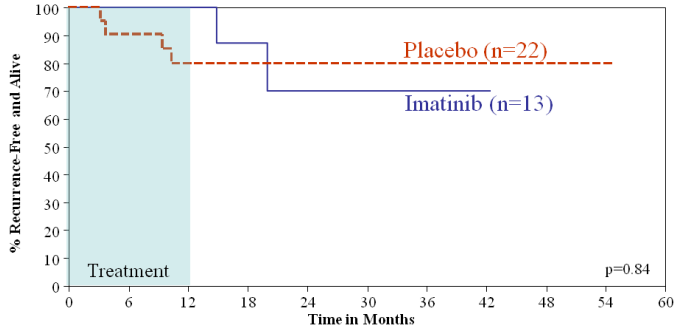


Corless CL et al. JCO 2010; 28(15s): suppl; abstract 10006.

RFS for Wildtype

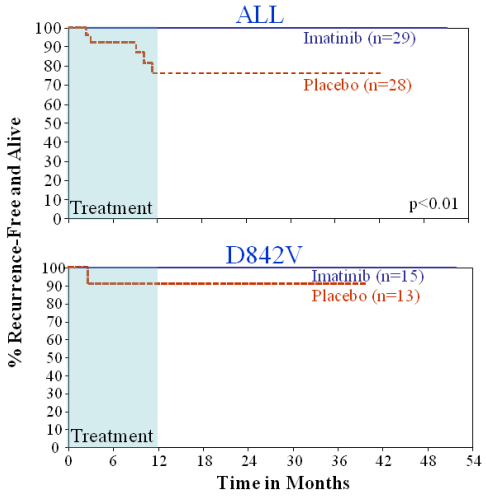


RFS for Exon 9



Corless CL et al. JCO 2010; 28(15s): suppl; abstract 10006.

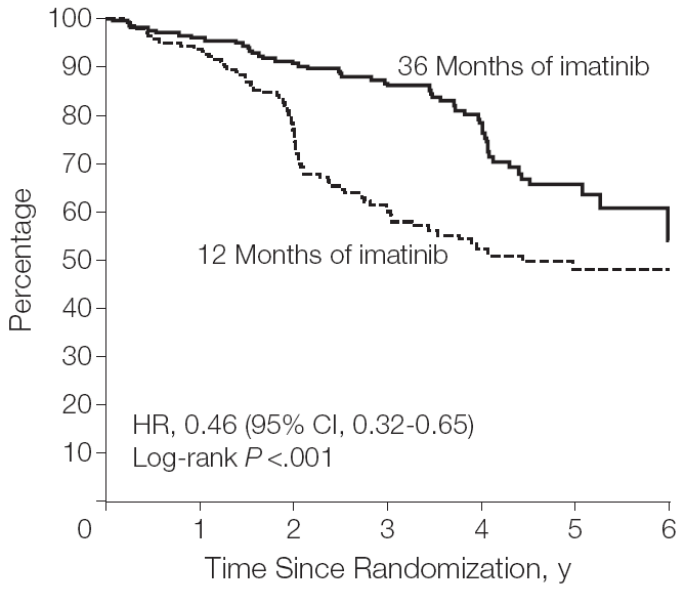
RFS for PDGFRA



Corless CL et al. JCO 2010; 28(15s): suppl; abstract 10006.

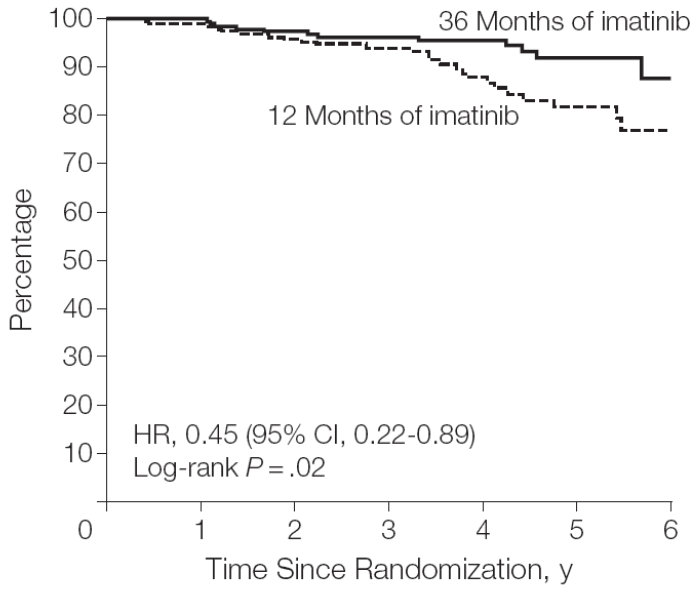
SSGXVIII/AIO: RFS and OS

A Recurrence-free survival: intention-to-treat population



No. of patients							
36 Months of imatinib	198	184	173	133	82	39	8
12 Months of imatinib	199	177	137	88	49	27	10

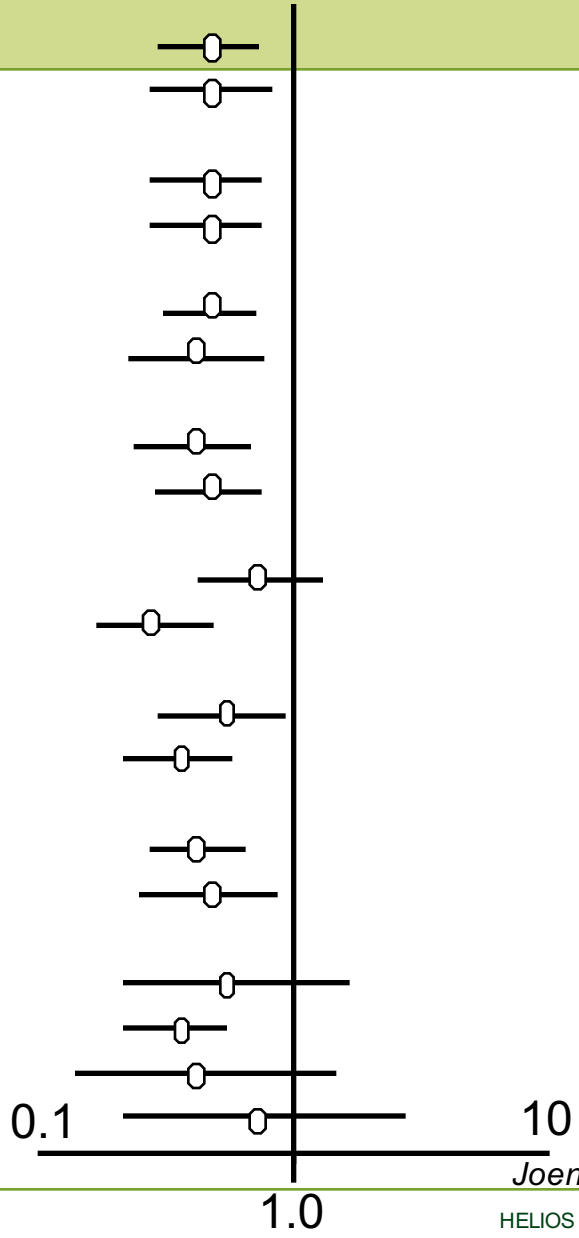
C Overall survival: intention-to-treat population



No. of patients							
36 Months of imatinib	198	192	184	152	100	56	13
12 Months of imatinib	199	188	176	140	87	46	20

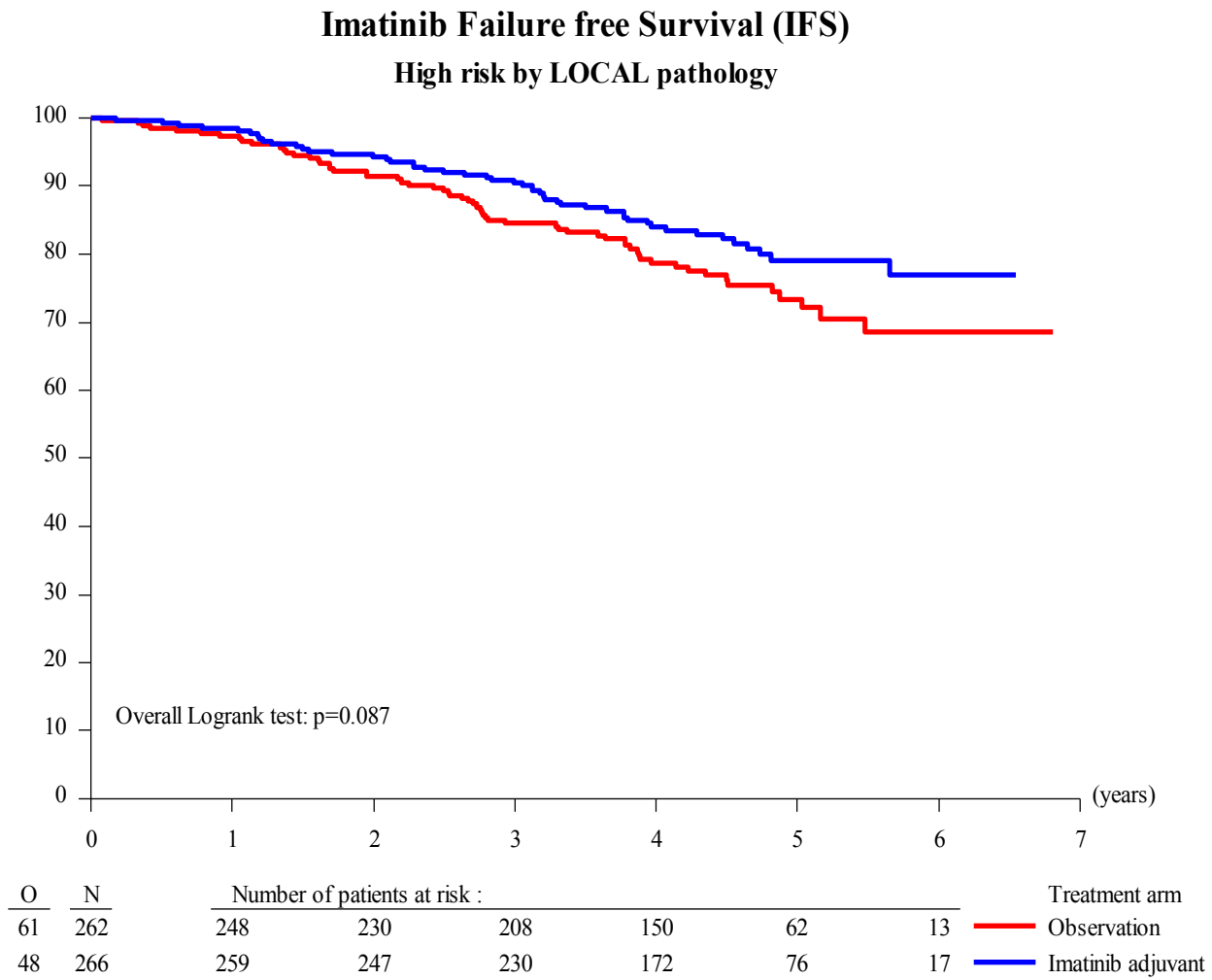
Joensuu, ..., Reichardt et al., JAMA 307:1265-1272, 2012

Subgroup	No. of patients	Hazard ratio (95% CI), RFS	*P* value
		36 mo better — *12 mo better*	
Age			
≤65	256	0.47 (0.30-0.74)	.001
>65	141	0.49 (0.28-0.85)	.01
Sex			
Male	201	0.46 (0.28-0.76)	.002
Female	196	0.46 (0.28-0.76)	.002
Tumor site			
Stomach	202	0.42 (0.23-0.78)	.006
Other	195	0.47 (0.31-0.73)	<.001
Tumor size			
≤ 10 cm	219	0.40 (0.24-0.69)	<.001
>10 cm	176	0.47 (0.29-0.76)	.002
Mitoses/50 HPF (local)			
≤ 10 mitoses	209	0.76 (0.43-1.32)	.33
> 10 mitoses	154	0.29 (0.17-0.50)	<.001
Mitoses/50 HPF (central)			
≤ 10 mitoses	238	0.53 (0.30-0.94)	.03
> 10 mitoses	133	0.36 (0.22-0.59)	<.001
Tumor rupture			
No	318	0.43 (0.28-0.66)	<.001
Yes	79	0.47 (0.25-0.89)	.02
Tumor mutation site			
KIT exon 9	26	0.62 (0.22-1.70)	.35
KIT exon 11	256	0.35 (0.22-0.56)	<.001
Wild type	33	0.41 (0.14-1.51)	.18
Other	51	0.78 (0.22-2.78)	.71



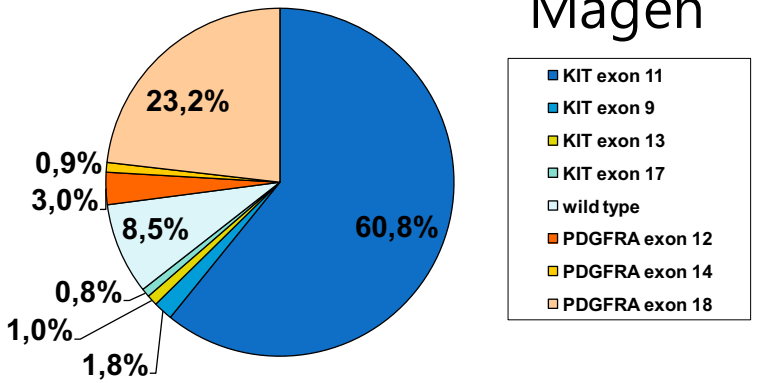
Joensuu, ..., Reichardt, JAMA 307:1265-1272, 2012

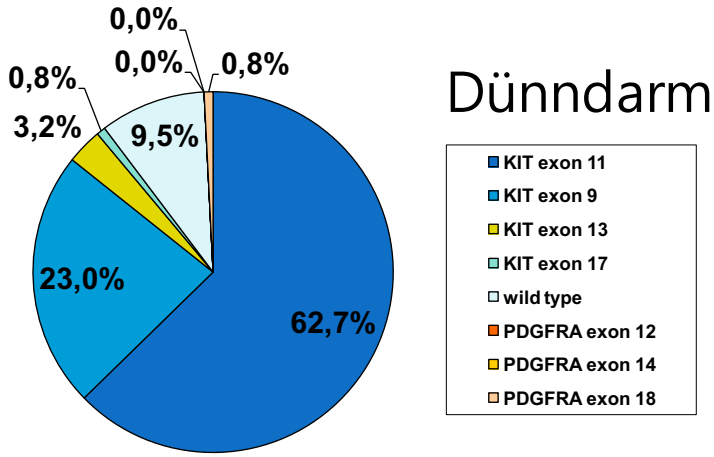
EORTC 62024: Imatinib failure-free survival in high risk

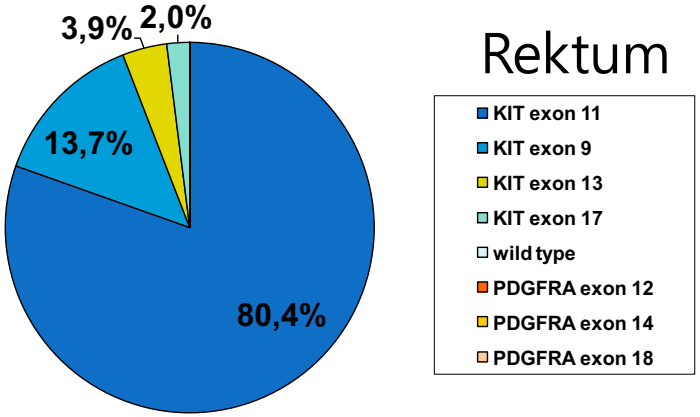


Casali et al., J Clin Oncol 31, 2013 (suppl; abstr 10500)

Correlation of *KIT*- and *PDGFRA*-Mutations and Primary Location





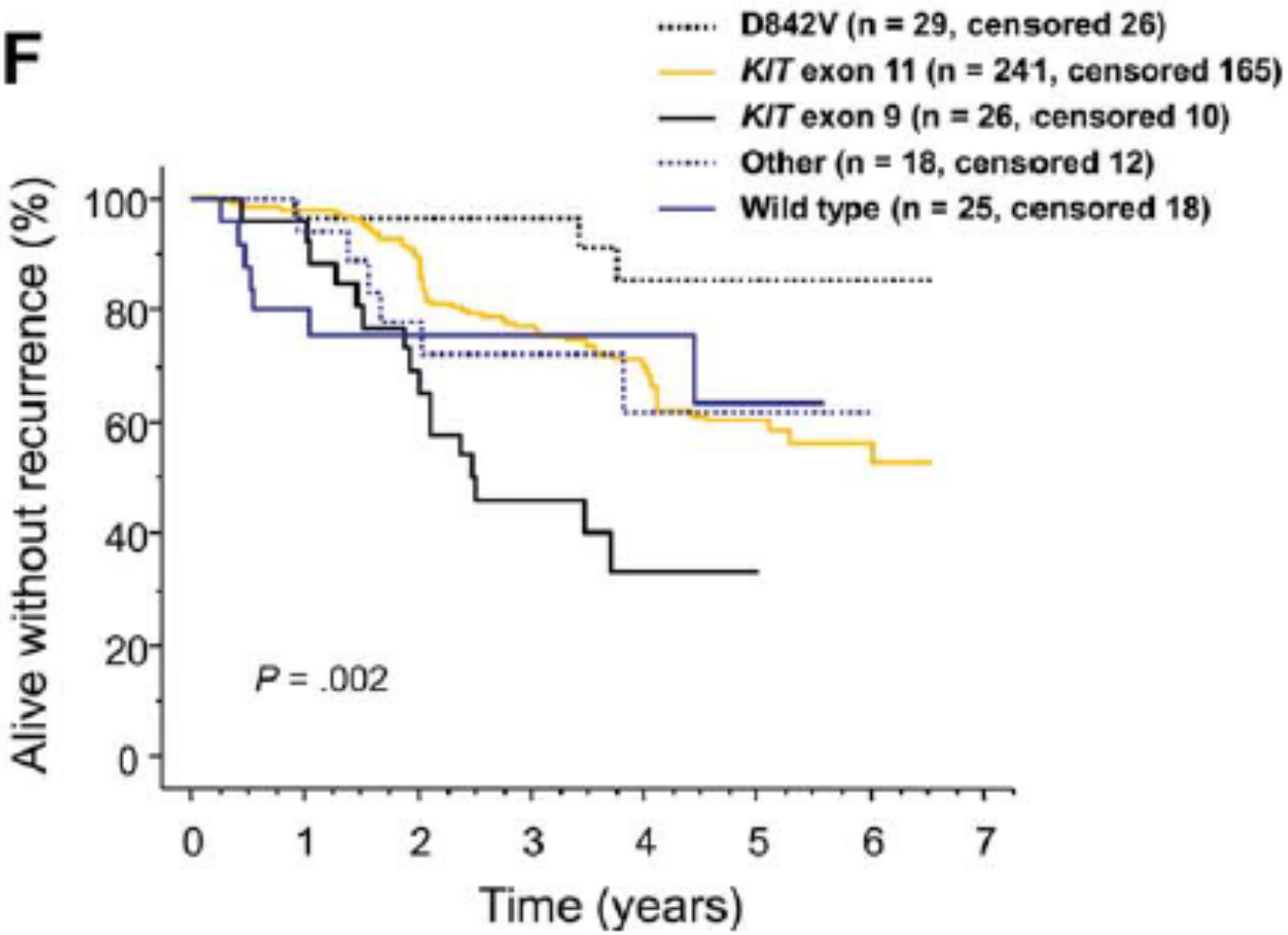


GSRCB* (n=1231)

*GSRCB = GIST and Sarcoma Registry Cologne/Bonn

Risk Factors for Gastrointestinal Stromal Tumor Recurrence in Patients Treated With Adjuvant Imatinib

Heikki Joensuu, MD[1]; Mikael Eriksson, MD[2]; Kirsten Sundby Hall, MD[3]; Jörg T. Hartmann, MD[4]; Daniel Pink, MD[5]; Jochen Schütte, MD[6]; Giuliano Ramadori, MD[7]; Peter Hohenberger, MD[8]; Justus Duyster, MD[9]; Salah-Eddin Al-Batran, MD[10]; Marcus Schlemmer, MD[11]; Sebastian Bauer, MD[12]; Eva Wardelmann, MD[13]; Maarit Sarlomo-Rikala, MD[14]; Bengt Nilsson, MD[15]; Harri Sihto, PhD[16]; Karla V. Ballman, PhD[17]; Mika Leinonen, MSci[18]; Ronald P. DeMatteo, MD[19]; and Peter Reichardt, MD[5]



Cancer August 1, 2014

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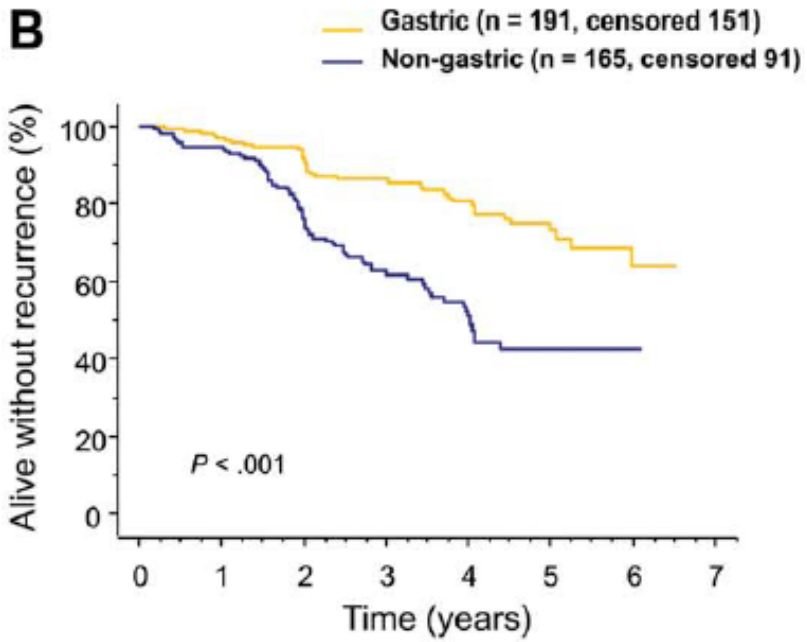

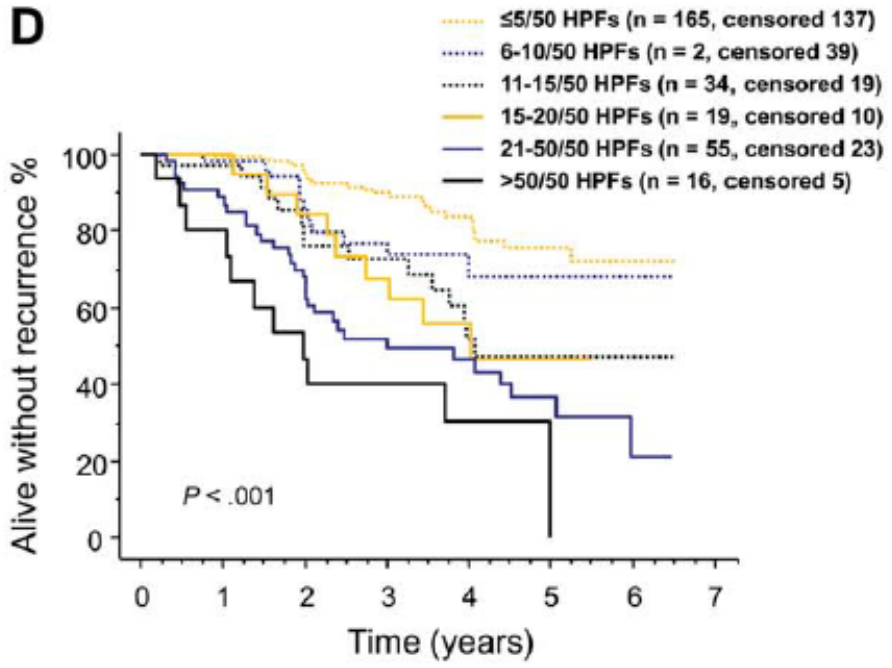

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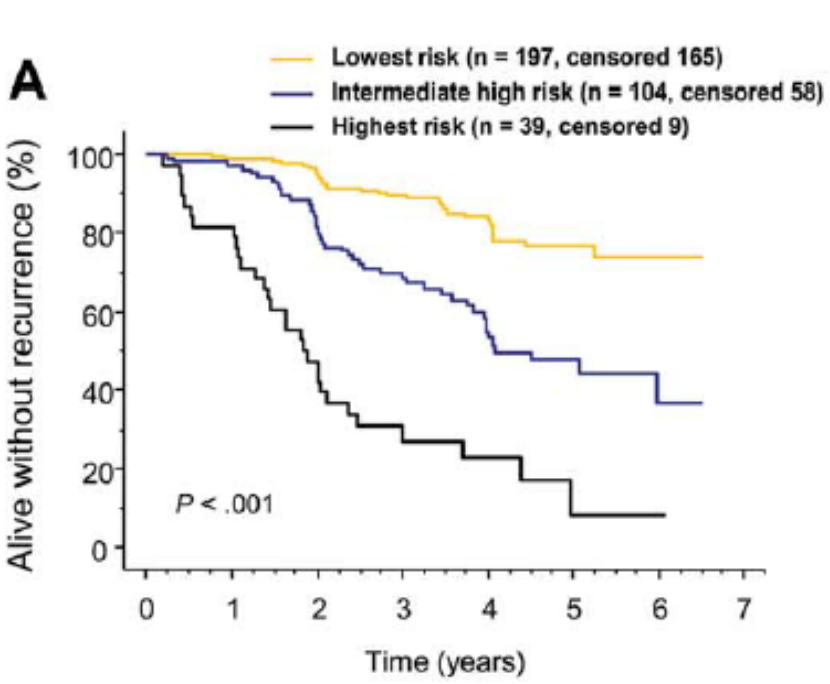
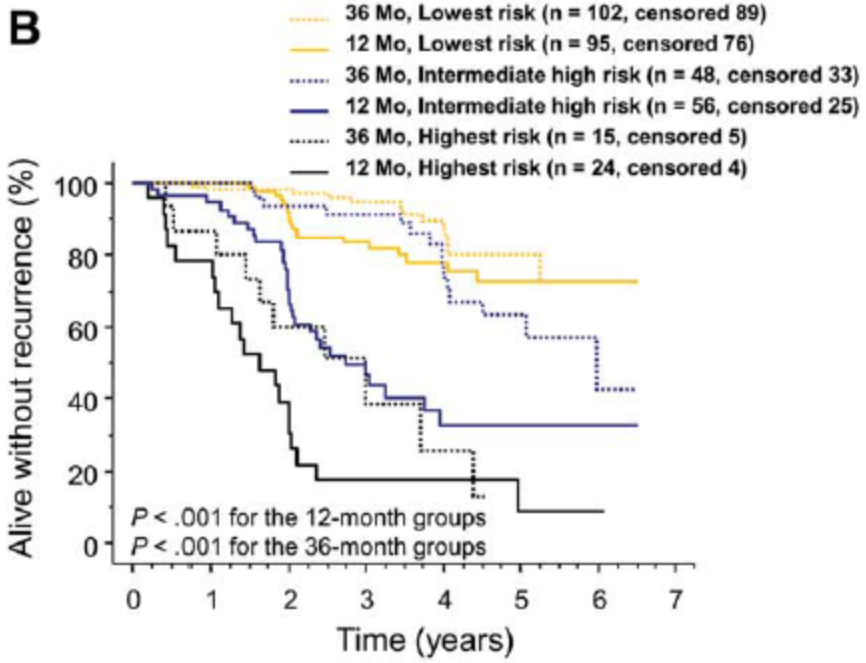


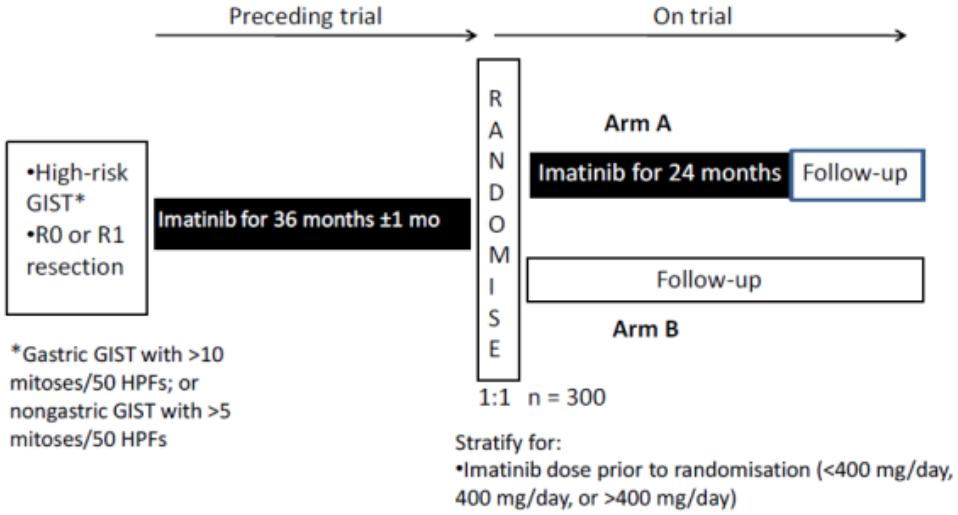


highest risk, gastric GIST with > 50 mitoses or non-gastric GIST with > 20 mitoses per 50 high-power fields).

Cancer August 1, 2014

Three versus five years of adjuvant imatinib as treatment of patients with operable GIST with a high risk for recurrence: A randomised phase III study

Trial design



NUMBER OF PATIENTS	300 patients to be randomised in 1:1 ratio, 150 to imatinib for further 24 months and 150 to stop imatinib.
RANDOMISATION	Central randomisation. At randomisation, the patients are stratified by the imatinib dose preceding randomisation (< 400 mg/day, 400 mg/day, or >400 mg/day). The centres will keep a log of patients who received the informed consent.